REMARKS

Reconsideration of this application is respectfully requested in view of the above amendments and the following remarks.

I. Interview Summary. Applicants gratefully acknowledge the courtesy shown by the Examiner during a telephonic interview conducted June 24, 2003. During the interview, a set of draft claims and all pending rejections were discussed. Agreement was reached on claim amendments that would address all pending rejections for indefiniteness, with one exception that is noted as follows. Agreement was not reached on language for claims 13, 22 and 34 that would be acceptable to the Examiner. The Examiner indicated that Applicants' arguments against rejections for alleged lack of enablement would be considered. No agreement, however, was reached on the enablement rejections set forth in the office action.

II. Drawings. Formal drawings are enclosed herewith. Pursuant to 37 C.F.R. § 1.84, color Fig. 3A-B and 5A-H are provided in triplicate. The specification has been amended to indicate the application includes color drawings and that copies of the patent with color drawings are available from the Patent and Trademark Office upon request and payment of the necessary fee. Black and white photographs that accurately depict the subject matter shown in the color photographs are no longer required. 1246 Official Gazette 106 (May 15, 2001).

III. Claim Status. Claims 1-48 are pending. Claims 1-4, 15, 22, 25, 34 and 37-39 have been amended. Claim 1 has been amended to clarify that the claimed method for making a chimeric mouse does not require that the xenogenic mammalian hepatocytes that are used to repopulate the degenerated liver be infected with a compatible hepatitis virus. Support for the amended claim is found in the specification at page 5, lines 5-10. Claims 2 and 3 have been amended to be consistent with amended base claim 1. Accordingly, claims 2 and 3 have

been amended to a method further comprising infecting the xenogenic mammalian hepatocytes of claim 1 with hepatitis virus prior to transplantation (claim 2) or following repopulation (claim 3). Support for amended claims 2 and 3 is found in the specification at page 5, lines 11-13. The scope of claims 2 and 3 is unchanged by the present amendment. The amendments to claims 1-3 are therefore supported by the application as filed. Accordingly, the amendments to claims 1-3 do not add new matter to the application.

Claims 13, 22 and 34 have been amended to replace the term "the [RAG-2] knockout gene" with the term "a [RAG-2] knockout mutation." Support for the amendments is found in the specification at page 4, lines 12-15. Accordingly, the amendments to claims 13, 22 and 34 do not add new matter to the application.

Claims 1, 15, 25, 37 and 39 have amended so that the steps of the respectivley claimed methods relate back to the preamble. Claim 39 has also been amended to replace the word "is" with the word "being," to conform with proper grammar. Claim 4 has been amended to conform to proper Markush group language. The foregoing amendments are changes in form only. The scope of the amended claims remains unchanged by the respective amendments. Accordingly, no new matter has been added to the application by these amendments.

IV. Claim rejections. The claim rejections are summarized and addressed as follows.

(i) Rejections under 35 U.S.C. § 112, second paragraph. Claims 1-7, 13-37, 39-42, 44-46 and 48 have been rejected as allegedly being indefinite. The Examiner alleges specifically that claims 1, 13, 15, 22, 25, 34, 37 and 39 include errors that require correction. In response, without conceding the Examiner's position, claims 1, 13, 15, 22, 25, 34, 37 and 39

have been amended. Each of the Examiner's objections to these claims is believed to have been addressed and overcome.

The Examiner additionally alleges that the meaning of the phrase "Recombination Activation Gene 2 (RAG-2) knockout gene" in claims 13, 22 and 34 is unclear. In response, the term "knockout gene" has been amended to "knockout mutation." Applicants submit that at the time the application was filed, one of ordinary skill in the art would understand that a knockout mutation describes a gene that has been inactivated by homologous recombination. Accordingly, the specification at page 4, lines 12-15 discloses the isolation of a mouse homozygous for the RAG-2 knockout mutation and cites Shinkai et al., (1992) *Cell*, **68**:855-867, (reference 22, which is of record in the file of the application). Shinkai et al. describe targeted disruption of the RAG-2 gene via homologous recombination (see Shinkai et al., Fig. 1 and text on page 856, first paragraph of "Results" section). The disruption leads to inactivation of the RAG-2 gene. Applicants have also enclosed copies of U.S. Patents No. 5,767,337; 5,777,195; and 5,866,756, whose filing dates predate the filing date of the present application. The '337 patent discloses that Apo E "knockout" animals refers to mice "whose endogenous Apo E gene has been disrupted by homologous recombination and which produce no functional Apo E of their own" (column 2, lines 35-38). The '195 patent discloses that a "knockout" mouse "contains within its genome a specific gene that has been inactivated by the method of gene targeting" (column 2, lines 37-39). The '756 patent discloses that "[k]nockout animals refers to animals whose native or endogenous DAT allele or alleles have been disrupted by homologous recombination and which produce no functional DAT of their own" (column 3, lines 10-13). Accordingly, Applicants submit that, as of the filing date of the instant application, based on the instant specification and the common understanding of the term "knockout" among those of ordinary skill in the art, one of ordinary

skill in the art would understand that a "RAG-2 knockout mutation" is a RAG-2 gene that has been inactivated by homologous recombination. No further definition is required. The phrase is therefore definite.

For the reasons set forth above, it is submitted that claims 1-7, 13-37, 39-42, 44-46 and 48 particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. The claims are therefore definite. Reconsideration of claims 1-7, 13-37, 39-42, 44-46 and 48 and withdrawal of all rejections thereof under 35 U.S.C. § 112, second paragraph is requested, accordingly.

(ii) Rejections under 35 U.S.C. § 112, first paragraph (enablement).

Claim 39 is rejected because the Examiner objects to the failure of the claim to recite hepatitis virus or infection of xenogenic mammalian hepatocytes with hepatitis virus. Applicants respectfully traverse. Claim 39 is directed to a method for creating an immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells that is repopulated with human hepatocytes. As set forth in the specification (see, e.g., page 9, line 15 through page 10, line 3 and Example14) and as is well known among those of ordinary skill in the art, human hepatocytes are capable of being infected with at least one compatible hepatitis virus. There is no disagreement that the claimed chimeric mouse created by the method of claim 39 is useful as a model for hepatitits. Such use is fully enabled by the specification. Having enabled at least one use for the chimeric mouse produced by the claimed method, Applicants need not enable any additional uses for the mouse produced by the method of claim 39. Accordingly, it would not have required undue experimentation for one of ordinary skill in the art to make and use the claimed method of claim 39.

Claims 1-6, 8-13, 15-22, 24-34 and 36-48 have been rejected because the Examiner alleges that the specification, while being enabling for the claims to the extent of the compatible hepatitis virus being hepadnavirus or hepatitis D coinfected with hepadnavirus, does not reasonably provide enablement for the claims with respect to any other hepatitis virus. The Examiner concludes that the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims. The Examiner's position is not well taken. Hence, the rejections are respectfully traversed.

Applicants first disagree with the Examiner's position that failure of Mercer et al. to obtain HCV infection in uPA hemizygous mice is sufficient to indicate unpredictability exists with regard to the ability of the chimeric mouse to support hepatitis infection that is directly correlated with the uPA transgene. Failure to obtain a given result by a single laboratory is not sufficient evidence to conclude that other researchers would not obtain a positive result of HCV infection in uPA hemizygous mice without undue experimentation. Furthermore, the Examiner has failed to establish that Mercer et al. failed to obtain HCV infection upon following the protocol set forth in the instant specification. Accordingly, Mercer et al.'s failure to obtain HCV infection in uPA hemizygous mice is insufficient to sustain a finding that it is not possible to obtain HCV infection in uPA hemizygous mice or that the instant specification has not enabled production of such mice.

Applicants traverse further on the ground that even if, arguendo, Mercer et al. is sufficient to establish an unpredictability with regard to uPA genotype and infection with certain hepatitis viruses, the instant specification is enabling for infection with any hepatitis virus because, at the time the application was filed, based on the teachings of the specification and the level of skill in the art, one of ordinary skill in the art would have been able to discern if a uPA

homozygous genotype was required for infection with certain types of hepatitis virus without undue experimentation. Applicants, position is based on the specifics that (1) the specification discloses homozygous uPA as a specific embodiment of the invention (2) the specification gives specific guidance on how to obtain homozygous uPA mice for repopulation with xenogenic hepatocytes and (3) at the time the invention was made it would have been routine for one of ordinary skill in the art to determine if a homozygous uPA genotype was required to support infection of a given strain of hepatitis virus.

Applicants do not concede that the results in Mercer et al. are sufficient evidence to conclude that the a hemizygous uPA genotype will not sustain infection with HCV. Even were this to be the case, however, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. MPEP 2164.08(b); *Atlas Powder Co. v E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 244 USPQ 409, 414 (Fed. Cir. 1984). Enablement is not precluded by the necessity for some experimentation. *In re Wands*, 858 F.2d 731, 736, 8 USPQ2d 1400, 1404 (Fed Cir 1988). The experimentation required to practice an invention must not be undue experimentation. "The key word [however], is 'undue,' not 'experimentation.'" *In re Wands*, 858 F.2d. at 737, 8 USPQ2d at 1404, quoting *In re Angstadt,* 537 F.2d 498 at 504, 190 USPQ 214 at 219 (CCPA 1976). The factors to be considered in determining whether undue experimentation is required to practice an invention include (1) the quantity of experimentation necessary, (2) the amount of direction of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Examiner maintains that the specification has *"failed to provide any guidance, working examples, or relevant teachings"* that would allow the skilled artisan to use hepatitis viruses other than those set forth in the instant specification when practicing the claimed invention (see Office Action at page 5, lines 6-9; emphasis added). The Examiner concludes that Mercer et al. suggest that "specific guidance with regard to the genotype of uPA transgene in chimeric mice *is necessary for creating models of hepatitis*." (see Office Action at page 5, lines 18-19; emphasis added). The Examiner's position is not well taken. Applicants need not provide working examples for all embodiments of the invention. The Examiner, moreover, has mis-characterized the level of guidance present in the instant specification, overstated the amount experimentation required to determine the uPA genotype that will support HCV infection (or infection of any hepatitis virus) and underestimated the level of skill in the art. For the reasons set forth below, the rejection should therefore be withdrawn.

The Examiner's position that the specification fails to give "any guidance" or "relevant teachings" with regard to the uPA genotype required for infection by any hepatitis virus is incorrect. The specification sets forth at page 10, lines 28-33, that "[a] preferred chimeric mouse of the invention is generated by repopulating the degenerated liver parenchyma of an immunetolerant mouse which is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene..." Accordingly, the specification gives clear guidance that an immunetolerant mouse homozygous for uPA is one of only two preferred embodiments for the chimeric mouse. The specification at page 11, line 17 through page 12, line 1, further sets forth methods for generating both hemizygous and homozygous uPA mice to be used as recipients for xenogenic mammalian hepatocytes. Accordingly, the specification sets forth specific "relevant" disclosure that homozygous uPA mice are a preferred embodiment of the

invention and methods for obtaining such homozygous uPA mice. Following the procedures set forth in the specification, one of ordinary skill in the art would routinely effect liver degeneration in both hemizygous and homozygous uPA mice. Hence, given the guidance set forth in the specification and the level of skill in the art at the time the application was filed, one of ordinary skill in the art could have practiced the full scope of the claims without undue experimentation.

The results reported in Mercer et al. support Applicants' position that all of the information required to practice the full scope of the claims is found within the four corners of the specification. Hence, Mercer et al. report that "[i]n initial experiments, homozygous SCID animals carrying the *Alb-uPA* transgene in hemizygous fashion were crossed" and transplanted with human hepatocytes (p. 927, col. 1). Mercer et al. further report that in a "pilot study" of 36 transplants, strong human-albumin signals were detected in the serum of 19 recipients (p. 927, col. 2), and that, subsequently, 4 of the 19 recipients were successfully infected with HCV (p. 928, Table 1). Hence, using a protocol crossing hemizygous uPA animals and repopulating both hemizygous and homozygous uPA animals (i.e., using a procedure disclosed in the instant specification), Mercer et al. successfully obtained HCV infection of homozygous uPA animals. Mercer et al. successfully obtained this result in a "pilot study," without any previous knowledge or "specific guidance" for using homozygous uPA animals, and without any further "experimentation" beyond the protocol set forth in the instant disclosure. Accordingly, contrary to the Examiner's position, the state of the art does not suggest that "specific guidance" with regard to the genotype of uPA transgene in chimeric mice is "necessary" for creating models of hepatitis. Mercer et al. establish that it was routine, indeed trivial, for one of ordinary skill in the art to test both homozygous and hemizygous uPA mice for infection with any type of hepatitis to optimize a particular embodiment of the invention. Choosing between only two embodiments

that constitute the total scope of the claim, and which can be practiced concurrently, and which routinely would be practiced concurrently by those skilled in the art, does not constitute "undue" experimentation. Accordingly, the rejection for lack of enablement should be withdrawn.

To support his position that the specification is not enabling, the Examiner cites *Genentech Inc. v Novo Nordisk A/S,* 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997). In *Genentech*, the Federal Circuit held invalid a claim directed to a method of producing a protein consisting essentially of amino acids 1-191 of human growth hormone (hGH). *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1004. The claim, in relevant part, called for (a) expressing human growth hormone "conjugate protein" with an "additional amino acid sequence which is specifically cleavable by enzymatic action," and (b) cleaving the conjugate protein extracellularly "by enzymatic action" to produce the protein consisting essentially of amino acids 1-191 of human growth hormone. The Federal Circuit found that the specification failed to enable the claim because the specification "does not describe in any detail whatsoever how to make hGH using cleavable fusion expression," and "no description of any specific cleavable conjugate protein appears." *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1004. The Court found further that "the specification does not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work." *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1004. The Court concluded that "when there is no disclosure of any of the conditions under which a process can be carried out, undue experimentation is required." *Genentech,* 108 F.3d at 1366, 42 USPQ2d at 1005.

The conditions that lead to invalidation of the claims in *Genentech*, however, are not present in the instant case. In *Genentech*, the specification failed to give any guidance on the sequence of a cleavable leader sequence, beyond the possibility that it might be cleavable by

trypsin *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1004. The present specification, in contrast, precisely describes the uPA homozygous mouse to be used in certain preferred embodiments. In *Genentech*, the amino acid sequences of the cleavable leader sequence could encompass an almost infinite number of amino acid sequences. *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1004-05. In the instant specification, the homozygous uPA mouse is one of only two possibilities for the uPA genotype. In *Genentech*, the Court noted that trypsin would not be expected to specifically cleave the leader from the conjugate protein and yield intact, useful proteins. *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1004. Hence, in Genentech the specification failed to give any reasonable guidance on operative embodiment of the claimed invention. In contrast, the instant specification specifically sets forth an embodiment of the invention that would be operative for infection with HCV — the uPA homozygous mouse. Accordingly, in *Genentech* the Court held that the claim could not be practiced without undue experimentation. As discussed above, the results reported in Mercer et al. are clear evidence that the full scope of the instant claims can be practiced without undue experimentation. The Court in *Genentech* set forth that "every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech,* 108 F.3d at 1366, 42 USPQ2d at 1005. The instant specification gives a precise description that enables members of the public to make and use a homozygous uPA mouse in for infection with any hepatitis virus. The instant specification therefore meets the standards set forth in *Genentech.*

For the reasons set fort above, Applicants submit that the specification enables one of ordinary skill in the art to make and use the invention commensurate in scope with the

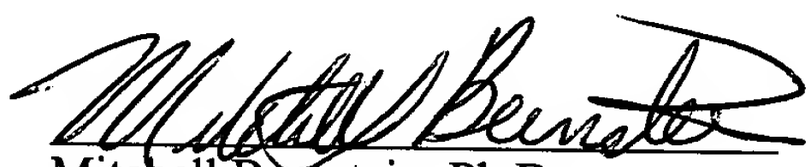
claims. Applicants request reconsideration of claims 1-6, 8-13, 15-22, 24-34 and 36-48 and withdrawal of all rejections thereof under 35 U.S.C. § 112, first paragraph, accordingly.

CONCLUSION

Therefore, in view of the above amendments and remarks, reconsideration of this application is respectfully requested It is earnestly solicited that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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